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13. SUPPLEMENTARY NOTES

14. ABSTRACT The goal of this project is to test our hypothesis that cellular context in which initiating oncogenic event occurs may have a dominant role over specific oncogene function in determining the molecular phenotype of each tumor. To test this hypothesis, we proposed to transform neural stem cells (NSCs) and neural progenitor cells (NPCs) in vivo by expressing an activated form of *Notch1* (N1ICD) or oncogenic *PIK3CA* (PIK3CAH1047R) in the developing mouse cerebellum, using cell type- specific Cre drivers *(En2-Cre* for NSCs and *Atoh1-creER* for NPCs).In the last year, we aged >10 *N1ICD;En2-Cre;p53-/-* mice and observed that while some of these mice became sick, none of them developed frank tumors, suggesting that En2+ population cannot be transformed by N1ICD expression. Therefore, we discontinued this mating and changed the Cre driver in NSCs to *hGFAP-cre* and *Sox2-CreER.* We are now aging *N1ICD;SOX2-CreER;p53-/-* and *N1ICD;hGFAP-cre;p53-/-* mice to collect tumors. In addition, we successfully intercrossed *PIK3CAH1047R (*a frequent mutant allele of PIK3CA observed in human cancer) to *Sox2CreER, Atoh1-creER*, and *p53-/-* strains to generate *PIK3CAH1047R;Sox2-creER;p53-/-* and *PIK3CAH1047R;Atoh1-CreER;p53-/-* mice. We are currently aging these mice for them to form medulloblastomas. Also as a backup, we started generating a YAP-induced medulloblastoma models. We anticipate collecting samples from either the *PIK3CAH1047R-* or *YAP*-induced models in the next year to complete this study.

15. SUBJECT TERMS cancer stem cells, medulloblastoma, targeted therapy, therapy resistance, pediatric cancer, brain tumor, Notch1, PIK3CA, cell of origin, molecular subtypes, neural stem cells, neural progenitor cells, tumor initiation.

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DoD Award W81XWH-14-1-0115 – Progress Report

1. INTRODUCTION:

The goal of this project is to test our **hypothesis that cells in various stages of maturation in the developing brain produce tumors with distinct biological characteristics when transformed by the same oncogenic event**. This hypothesis was based on our observations that certain oncogenes, such as *Id2* and constitutively active *Notch1* (N1ICD), induced DNA damage and apoptosis when activated in neural stem cells (NSCs) *in vivo* but had no observable effect when activated in neural progenitor cells (NPCs), immediate progenies of NSCs. These observations indicate that epigenetic changes that occur during NSC-NPC transition somehow block oncogenes from functioning in NPCs. In other words, cellular context in which tumors initiate may have a dominant role over some oncogene function.

In addition, we recently reported that cancer stem cells (CSCs)- stem cell like cells in tumors that have stem cell properties and tumor initiating ability- retain epigenetic memories of their cells of origin (Chow et al., 2014). We showed that CSCs derived from NSCs and NPCs depend on different mitogenic and survival pathways, even when they are transformed by the same oncogene *in vivo*. This finding has multiple implications: one of the most significant being that targeted therapies selected based on bulk tumor cell analysis may be ineffective in eradicating CSCs. We showed in a SHH medulloblastoma model that responsiveness of CSCs to SHH inhibitors therapies varied greatly depending on the cell type in which tumor initiation occurred *in vivo*. If this novel discovery were generalizable, it would suggest that we will need to analyze CSCs (rare cells in the tumor) and not just the bulk tumor cells (current practice) to identify therapy combinations that will eradicate both CSCs and non-stem (bulk) tumor cells.

To directly test whether the cell-of-origin or the activated oncogene itself has more dominant role in determining molecular phenotypes of bulk tumor cells and CSCs, we proposed to generate and analyze spontaneous medulloblastomas by transforming NSCs and NPCs by expression of an activated form of *Notch1* (N1ICD) or oncogenic *PIK3CA* in the developing mouse cerebellum, using cell type- specific Cre drivers *(En2-Cre for NSCs and Atoh1-creER for NPCs).*

2. KEYWORDS:

cancer stem cells, medulloblastoma, targeted therapy, therapy resistance, pediatric cancer, brain tumor, Notch1, PIK3CA, cell of origin, molecular subtypes, neural stem cells, neural progenitor cells, tumor initiation.

3. ACCOMPLISHMENTS:

Major goals of the project:

The stated goals of this project are to: 1) test the general applicability of our observation across multiple tumor models in which different oncogenic events initiate tumor formation and 2) test our hypothesis that cells in different stages of maturation in developing organs produce tumors with distinct molecular and cellular characteristics even when the initiating oncogenic event is the same.

To test the general applicability of our novel hypothesis, we will transform NSCs and NPCs in the developing mouse cerebellum using cell stage- specific Cre drivers (*En2-Cre or GFAP-cre for NSCs* and *Atoh1-creER or Olig2-cre for NPCs*). We will express activated *Notch1* (N1ICD) or an oncogenic mutant form of PIK3CA in *p53*-/- brains. We will analyze both bulk tumor cells and CSCs from each of these models and compare their molecular and cellular characteristics, including CSC culture behavior and AKT activation. We will also compare molecular profiles of bulk tumors and CSCs of these tumors to determine whether the oncogene or the cellular context plays a more dominant role in driving the molecular phenotypes by unsupervised clustering analyses.

What was accomplished:

During this period, we focused on generating new models of medulloblastoma by activating N1ICD and PIK3CA in cerebellar NSCs and NPCs in the developing mouse brain.

N1ICD models:

We previously published that activated Notch1 (N1ICD) expression in the developing brain induces apoptosis due to DNA damage and p53 activation. When p53 is genetically deleted, ~40% of *N1ICD;GFAP-cre;p53-/-* mice developed spontaneous medulloblastomas (Natarajan et al., 2013). To generate medulloblastomas that arise from transformed NSCs, we intercrossed *N1ICD, En2-Cre*, and *p53* strains to generate *N1ICD;En2-cre;p53-/-* mice. To date, we have generated more than eight ***N1ICD;En2-cre;p53-/-* mice**; however, none of them formed medulloblastomas. The triple transgenic mice are viable, although they have shorter life span than wildtype mice. They appear to succumb to neurological defects.

To activate the same transgene in NPCs in the external granule layer (EGL), we intercrossed *N1ICD, Atoh1-CreER,* and *p53* strains to generate ***N1ICD;Atoh1-CreER;p53-/-*.** We activated the transgene in these mice by treating p3-5 pups with Tamoxifen. Thus far, we have not observed any medulloblastomas from these mice. We are currently aging these mice to collect medulloblastoma samples for analysis.

PIK3CA models:

Because the reviewers had asked for (and DoD approved) switching out *Xrcc2-/-*induced medulloblastoma model (proposed in the original submission) with PIK3CA-induced medulloblastoma model, we are behind schedule in terms of generating tumors. We first analyzed the effects of PIK3CA* expression in different cellular compartments in the developing brain. As shown in Figure 1, expression of mutant PIK3CA* in the developing embryo brain (by Nestin-Cre) induced severe dysplasia (Fig 1A, B), and ***PIK3CA*;Nestin-cre*** mice died with hydrocephalus by weaning age. We validated elevated PIK3CA signaling in these brains by increased pAKT and pS6 expression in transgenic brains (Fig 1C, D). *PIK3CA** expression in slightly more mature neuroepithelium (by GFAP-Cre) induced milder dysplasia with prominent rosette formation in the neuroepithelium in ***PIK3CA*;hGFAP-cre*** brains (Fig 1E), but still resulted in hydrocephalus and lethality by weaning age. Interestingly, PIK3CA* expression in committed neural progenitors (by Ngn1-cre) did not result in dysplasia although the *PIK3CA*;Ngn1-cre* brains are megacephalic, Fig 1F, G). These mice also died around 2 months of age of unknown reasons. These analyses showed that the PIK3CA* transgenic model we use is functional and that oncogenic PIK3CA expression in the developing brain affects proliferation and differentiation, as anticipated.

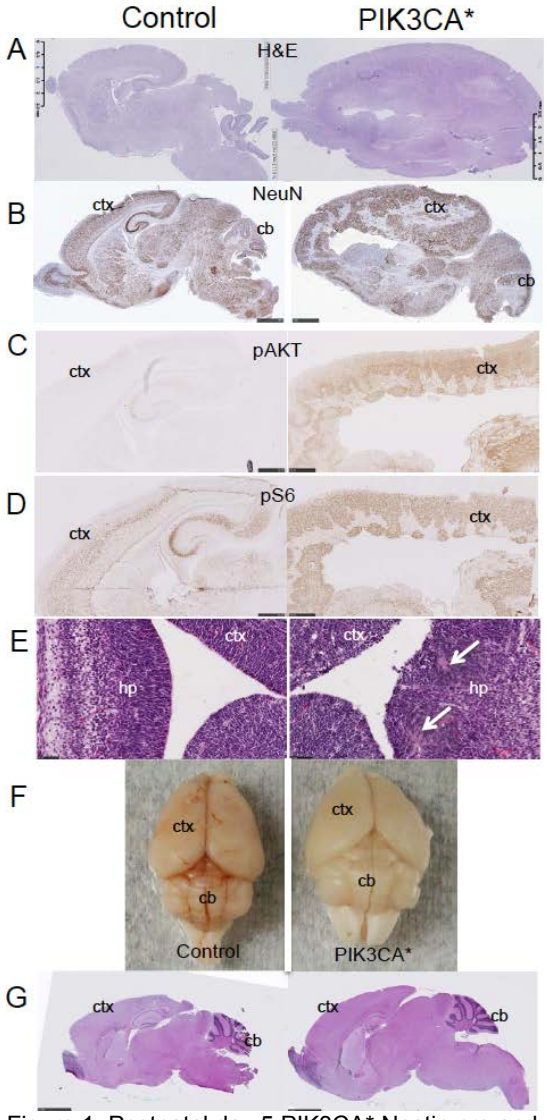

Figure 1. Postnatal day 5 PIK3CA*;Nestin-cre and control brains stained with (A) H&E, (B) NeuN, a neuronal marker, (C) pAKT, and (D) pS6. (E) E15.5 PIK3CA*;GFAP-Cre brain stained with H&E showing rosettes in neuroepithelium. Gross (F) and H&E (G) stained images of control (left) and PIK3CA*;Ngn1-cre brain (right) at 2 months showing megacephaly. Abb: ctx=cortex, cb= cerebellum, hp= hippocampus

To circumvent early lethality associated with PIK3CA* expression, we made two modifications to our approach. First, we used a different and more clinically-relevant allele of PIK3CA, *PIK3CAH1047R*, to activate the PI3K pathway. Unfortunately, ***PIK3CAH1047R;Nestin-cre*** mice die soon after birth. They are born with obvious megacephaly (not shown). To circumvent this early developmental defect, we switched our Cre driver to *Sox2-CreER*. In these mice, Cre is activated in *Sox2*+ cells only when treated with Tamoxifen. We generated ***PIK3CAH1047R;Sox2CreER*** mice and treated them with Tamoxifen at p3-p5. We are aging these mice to test whether they develop spontaneous tumors.

To generate new medulloblastoma models induced by PIK3CA* expression, we directed PIK3CA* expression in the developing cerebellum by mating PIK3CA* mice to the *En2-Cre* driver. *En2-Cre* is active in mid/hind brain neuroepithelium from very early on (E9.0 onwards). ***PIK3CA*;En2-cre*** mice are viable (>240 days) but they have hypoplastic vermis and hyperplastic superior collilus (Fig 2A), suggesting that the effects of PIK3CA* expression is cell context-specific. Furthermore, cerebellar hemispheres were disorganized (Fig 2B), and marker analyses for activated PI3K pathway (pS6, Fig 2C), purkinje neurons (calbindin, Fig 2D), and proliferation (Ki67, Fig 2E) suggest that aberrant elevation of PIK3CA signaling affects cell proliferation/survival, differentiation and migration. Together, these results indicate that PIK3CA* expression in early cerebellar stem cells may result in oncogene-induced apoptosis or senescence at an early age. To test whether PIK3CA* expression induced p-53 dependent apoptosis and whether blocking this process induces tumor formation, we generated ***PIK3CA*;En2-cre;p53-/-.*** Again, these mice are viable and no tumor formation has been observed yet.

We are currently analyzing PIK3CAH1047R* expression in cerebellar NPCs, using *Atoh1-CreER* inducible driver in EGL progenitor cells. We will determine whether embryonic and postnatal day EGL progenitor cells respond similarly as NCSs to PIK3CAH1047R* expression and whether deleting the p53 tumor suppressor gene function will result in spontaneous medulloblastoma formation.

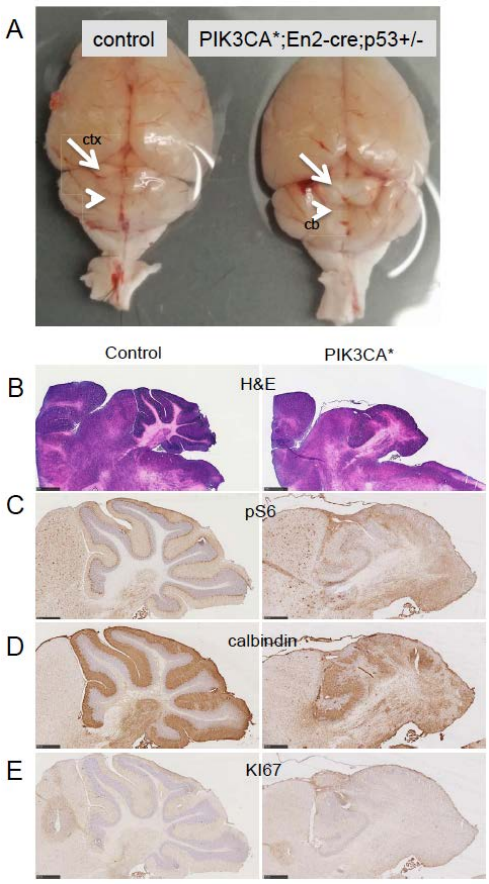

Figure 2. Littermate control and PIK3CA*'En2-cre;p53+/- brains at 6 months (A) gross images, (B) H&E, (C) pS6, (D) calbindin, and (E) KI67 staining. Arrows in A point to inferior colliculus, arrowheads point to vermis.

Alternative models of medulloblastoma:
Despite our Continued efforts to produce PIK3CA-* induced medulloblastomas, so far, we have not observed any localized tumors in the cerebellum. Since PIK3CA* is a strong allele of PIK3CA (truncation mutation), we tested a common point mutation in PIK3CA gene in human tumors, PIK3CA H1047R. We are currently crossing this strain to various Cre drivers described above.

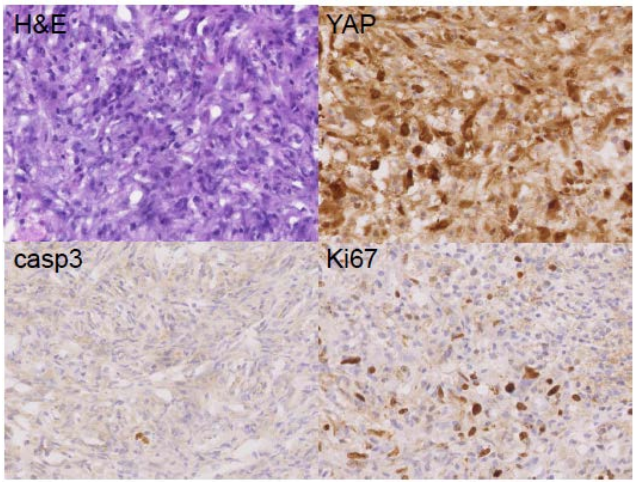

Figure 3. YapS5A;AtohCreER medulloblastoma, stained with H&E or antibodies against YAP, cleaved Caspase 3, and Ki67 as indicated.

In parallel, we are developing a new medulloblastoma model induced by expression of constitutively active YAP. YAP is a transcriptional effector of the Hippo pathway and its expression is elevated in SHH subgroup of human medulloblastomas. Interestingly, it is amplified in a subset of SHH medulloblastomas, suggesting that it may be an oncogene. To test this directly, we expressed YapS5A (constitutively active form of YAP) in the developing cerebellum by treating ***YapS5A;AtohCreER*** mice with Tamoxifen at p3-p5. One of the three ***YapS5A;AtohCreER*** mice developed a spontaneous medulloblastoma (Fig. 3). We propose to study YapS5A-induced tumors if we cannot generate PIK3CA-induced medulloblastomas.

Training opportunities: N/A

Results dissemination: Nothing to report

Plan for the no-cost extension period:

We will continue to intercross and generate triple transgenic mice and age them to collect at least 10 tumors of each genotype (*N1ICD;Atoh1-CreER;p53, N1ICD;Sox2-Cre;p53, PIK3CAH1047R;Atoh1-CreER;p53,* and *PIK3CAH1047R;Sox2-Cre;p53*). If we do not observe significant tumor incidences in PIK3CA-induced models in the next 6 months, we will replace those with YapS5A induced models. We will analyze their transcriptomes to determine whether the cell of origin or the oncogene function plays a dominant role in determining the molecular phenotypes of medulloblastomas.

4. IMPACT:

Impact of the principal and other disciplines: Nothing to report

Impact on technology transfer: Nothing to report

Impact on Society: Nothing to report

5. CHANGES/PROBLEMS:

Problems or delays:

This project is a little delayed due to two main reasons. One, we observed higher than anticipated incidence of sarcoma formation from mice in p53+/- or p53-/- backgrounds. We had to sacrifice triple transgenic mice before they could form brain tumors; hence, we are behind schedule in terms of collecting spontaneous medulloblastomas. To bypass this limitation, we started crossing floxed-p53 mice to N1ICD and PIK3CA* mice so that we can delete p53 only in cells that are also expressing N1ICD or PPIK3CA* oncogenes in the brain. The second reason for the delay is that the reviewers had asked us to change the second oncogenic event (*Xrcc2* deletion) to a more clinically–relevant genetic event (we chose PIK3CA mutation). This change was approved pre-award by DoD. However, since this is a new model, we had to do more model characterization than anticipated, which caused some delay. We continue to mate these mice to generate transgenic mice; however, if the tumor incidence rate is low or the latency is too long, we will switch the model to YapS5A induced models.

Changes with significant impact on expenditure: Nothing to report

Changes to human subjects, animals, or agents: Nothing to report

6. PRODUCTS: Nothing to report

7. PARTICIPATION & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name	Kyuson Yun
Project Role	Principal Investigator
Researcher Identifier (NIH Commons ID)	KYUSONYUN
Nearest person month worked	6
Contribution to Project	overall supervision, experimental design and analysis.
Funding Support	N/A

Name	Kin-Hoe Chow
Project Role	Postdoctoral Associate
Researcher Identifier (NIH Commons ID)	KINHOECHOW
Nearest person month worked	2
Contribution to Project	generation and analysis of new medulloblastoma models
Funding Support	N/A

Name	Keiko Yamamoto
Project Role	Research Assistant
Researcher Identifier	N/A
Nearest person month worked	2
Contribution to Project	animal husbandry to generate new models of medulloblastoma
Funding Support	N/A

Name	Rachael McMinimy
Project Role	Co-Op Associate
Researcher Identifier	N/A
Nearest person month worked	2
Contribution to Project	histological analysis of new medulloblastoma models
Funding Support	N/A

Name	Ryota Nakada
Project Role	Co-Op Associate
Researcher Identifier	N/A
Nearest person month worked	1
Contribution to Project	PCR genotyping to set up appropriate mating and histological analysis of mutant brains.
Funding Support	N/A

Has there been a change in the active other support of the PD/PIs or senior/key personnel since the last reporting period?

Yes. Dr. Yun's current other support is detailed below (changes are indicated in italics.)

Yun, Kyuson

Active

Supporting Agency:	NIH/NCI 5 R21 CA191848-02	**PI:**	Chuang
Project Title:	Dissection of Tumor Evolution Using Patient-Derived Xenografts		
Role:	Co-Investigator	**Effort:**	0.60 CM
Entire Project:	07/01/2015 - 06/30/2017	$531,399	
Current Year:	07/01/2016 - 06/30/2017	$204,100	
Project Goals:	The goal of this exploratory study is to test and apply patient-derived xenografts (PDX) as an improved system to quantify rates of tumor subclonal population evolution.		
Specific Aims:	1: Spatial and Temporal Dissection of Subclonal Heterogeneity in Breast Cancer Xenografts - a. Characterization of spatially and temporally separated breast cancer xenografts; b. Computational identification and analysis of subpopulations; c. Validation of subpopulations by single-cell sequencing; 2: Determination of Subclonal Evolution During Drug Treatment - a. Genomic and histological characterization of spatially and temporally separated xenografts under drug treatment; b. Identification, analysis, and validation of subpopulations relevant to therapy response.		
Overlap:	None		
Contracting/ Grants Officer:	Sarah M. Lee - sarah.lee@nih.gov		

	Donaldson Charitable Trust DONALDSON-FY15-KY-01	***PI:***	*Yun*
Project Title:	*Understanding the earliest steps in cancer formation*		
Role:	*Principal Investigator*	***Effort:***	*3.60 CM*
Entire Project:	*12/07/2015 - 12/06/2016*	*$133,875*	
Current Year:	*12/07/2015 - 12/06/2016*	*$133,875*	
Project Goals:	*The goal of this project is to test they hypothesis that different epigeitic ststates of the stem and progenitor cells either allow or suppress oncogenes to initiate tumors in vivo.*		
Specific Aims:	*1. Map and compare open chromatin regions in neural stem cells and neural progenitor cells from the developoing mouse brain to eludicate differential vulnerabilities of these two populations to oncogene induced DNA damage and transformation*		
Overlap:	*None*		
Contracting/ Grants Officer:	*Allen Mast, Corporate Trustee*		

Supporting Agency:	*The Jackson Laboratory Director's Innovation Fund JAX-BIDMC-Pilot-FY15-Choi-Yun*	***PI:***	*Choi, Yun*
Project Title:	*Development of Brain Tumor-Targeted Theragnostic Agents for Clinical Translation*		
Role:	*Principal Investigator*	***Effort:***	*0.60 CM*
Entire Project:	*09/01/2015 - 08/31/2016*	*$45,000*	
Current Year:	*09/01/2015 - 08/31/2016*	*$45,000*	
Project Goals:	*The goal of this project is to develop a bifunctional theragnostic agent to provide surgeons with real-time image guidance during brain tumor surgery and induce cancer cell death in distantly infiltrated tumor cells that cannot be resected.*		
Specific Aims:	*1. Validate general applicability and clinical potential of SP66 as a theragnostic agent by measuring tumor uptake in PDX GBM models and a spontaneous mouse medulloblastoma model; 2. Evaluate the therapeutic potential of SP66 in vitro and in vivo.*		
Overlap:	*None*		
Contracting/ Grants Officer:	*Rita Poirier - rita.poirier@jax.org*		

Supporting Agency:	*Maine Medical Center NSI-1101-001 2015*	***PI:***	*Emery*
Project Title:	*Inhibition of Stem Cell Pathways in a Patient-Derived GMB Tumor Model System*		
Role:	*Consortium PI*	***Effort:***	*0.12 CM*
Entire Project:	*10/01/2015 - 09/30/2016*	*$15,000*	
Current Year:	*10/01/2015 - 09/30/2016*	*$15,000*	
Project Goals:	*The goal of this study is to elucidate the role of ABCG2 in glioma stem cells.*		
Specific Aims:	*1. evaluate the therapeutic potential of ABCG2 inhibitors on primary GBM tumorspheres*		
Overlap:	*None*		
Contracting/ Grants Officer:	*Michele Locker - lockem@mmc.org*		
Supporting Agency:	*St. Baldrick's Foundation*	***PI:***	*Yun*
Project Title:	*Preclinical Evaluation of Treating SHH Medulloblastomas with Yap1 Inhibitors*		
Role:	*Principal Investigator*	***Effort:***	*0.12 CM*
Entire Project:	*06/12/2016 - 08/12/2016*	*$5,000*	
Current Year:	*06/12/2016 - 08/12/2016*	*$5,000*	
Project Goals:	*These funds are to support a summer fellowship position in Dr. Yun's laboratory.*		
Specific Aims:	*N/A*		
Overlap:	*None*		
Contracting/ Grants Officer:	*Liz Jackson - liz@stbaldricks.org*		

Submitted

Supporting Agency:	NIH/NCI 1 R01 CA195700-01A1	**PI:**	Yun
Project Title:	Validation and Generation of Matching GBM PDX and Tumorsphere Cultures as Translational Research Tools		
Role:	Principal Investigator	**Effort:**	4.00 CM
Entire Project:	09/01/2016 - 08/31/2019	$2,404,222	
Current Year:	09/01/2016 - 08/31/2017	$796,199	
Project Goals:	Our goals of this project are to elucidate inherent biases in patient-derived xenograft (PDX) and tumorsphere models to enable more comprehensive modeling of Glioblastoma multiforme (GBM) in the future, and to validate our optimized ex vivo tumor slice system using PDX models as a clinically relevant tool for translational research.		
Specific Aims:	1. Elucidate selective bias in establishing and propagating PDX models of human GBMs; 2. Determine the heterogeneity of tumor- initiating and sphere-forming cells in human GBMs; 3. Validate ex vivo tumor slice cultures from GBM PDX models as a platform for translational research.		
Overlap:	None		
Contracting/ Grants Officer:	Mariam Eljanne - eljannem@mail.nih.gov		

Completed

Supporting Agency:	Maine Technology Institute SG5424	**PI:**	Yun
Project Title:	Development of Novel Anti-cancer Agents		
Role:	Principal Investigator	**Effort:**	0.12 CM
Entire Project:	07/01/2015 - 06/30/2016	$25,000	

Supporting Agency:	American Brain Tumor Association	**PI:**	Yun, Kyuson
Project Title:	Predicting Therapy Resistance Based on Cancer Stem Cell Phenotypes		
Role:	Principal Investigator	**Effort:**	0.60 CM
Entire Project:	07/01/2013 - 06/30/2014	$50,000	

Supporting Agency:	Maine Cancer Foundation	**PI:**	Yun, Kyuson
Project Title:	Development of Ex Vivo Organotypic Slice Culture Systems for Cancer Studies		
Role:	Principal Investigator	**Effort:**	1.20 CM
Entire Project:	07/01/2013 - 06/30/2015	$164,686	

Supporting Agency:	The Jackson Laboratory Director's Innovation Fund	**PI:**	Yun, Kyuson
Project Title:	Postdoctoral Associate Support		
Role:	Principal Investigator	**Effort:**	0.12 CM
Entire Project:	08/01/2013 - 07/31/2014	$160,000	

Supporting Agency:	American Cancer Society 118571-RSG-10-042-01-DDC	**PI:**	Yun, Kyuson
Project Title:	S100a4 Expression and Function in Brain Cancer Stem Cells		
Role:	Principal Investigator	**Effort:**	2.40 CM
Entire Project:	01/01/2010 - 12/31/2014	$720,000	

Supporting Agency:	Oliver S. and Jennie R. Donaldson Charitable Trust	**PI:**	Yun, Kyuson
Project Title:	Cancer Risk Factors and Cell Type: Elucidating Brain Cancer Formation		
Role:	Principal Investigator	**Effort:**	1.20 CM
Entire Project:	12/17/2013 - 12/16/2015	$325,000	

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS: none

9. APPENDICES: N/A